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Aspirin Dose and Six-Month Outcome After an Acute Coronary Syndrome

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OBJECTIVES This study was designed to compare the efficacy of low and intermediate aspirin doses in acute coronary syndromes.

BACKGROUND Little is known of the comparative efficacy of low and intermediate aspirin doses in this setting.

METHODS We compared six-month death, myocardial infarction (MI), and stroke in patients with unstable angina or acute MI discharged while receiving low (<150 mg) or intermediate (≥150 mg) aspirin therapy in the GUSTO IIb and PURSUIT trials (n = 20,521). We used multivariable analysis and performed a propensity analysis in order to adjust for baseline imbalances between the groups.

RESULTS Aspirin doses <150 mg were prescribed to 29.9% (6,128) of patients. By six months, 6.4% of the patients (1,310 of 20,521) had a primary event, 6.2% of the patients receiving <150 mg and 6.6% of the patients receiving aspirin doses ≥150 mg (hazard ratio [HR] 1.06 [95% confidence interval (CI) 0.94 to 1.19], p = 0.35). After adjusting for baseline imbalances and the propensity score for discharge aspirin dose, there was no effect of aspirin dose on the composite end point at six months (HR 0.92 [95% CI 0.79 to 1.07], p = 0.28). However, the higher aspirin dose was associated with a reduction in six-month MI (HR 0.79 [95% CI 0.64 to 0.98], p = 0.03). The outcome was similar when patients were matched on the basis of the propensity score for aspirin dose (HR for death/MI/stroke 0.94 [95% CI 0.80 to 1.12], p = 0.51), although stroke occurred significantly more frequently among patients receiving the higher aspirin dose (HR 1.74 [95% CI 1.01 to 3.02] p = 0.05) and the effect on MI was no longer apparent.

CONCLUSIONS Although these data are non-randomized, they suggest that the aspirin dose upon discharge may influence the clinical course after unstable angina or acute MI. (J Am Coll Cardiol 2004;43:972–8) © 2004 by the American College of Cardiology Foundation

The antiplatelet agent aspirin provides marked protection from vascular events in a broad spectrum of patients with atherosclerotic disease. In a recent meta-analysis of 287 trials in more than 210,000 patients, aspirin prevented 25 serious vascular events (vascular death, myocardial infarction [MI], or stroke) per thousand patients treated (1). The dose of aspirin studied in these trials varied from 20 mg to 1,500 mg, and the proportional reduction in risk was similar for doses of 75 to 150 mg, 160 to 325 mg, and 500 to 1,500 mg. Aspirin doses between 75 and 325 mg are currently recommended by the European Heart Association, the American College of Cardiology, and the American Heart Association for the management of patients with acute coronary syndromes (ACS) (2,3). Doses in the lower end of this range are often preferred to limit gastrointestinal side effects (4). However, little is known of the comparative efficacy of aspirin doses within this range in patients with ACS. The evidence to support the equivalent efficacy of aspirin doses between 75 and 325 mg is mainly drawn from indirect comparisons between trials of different aspirin dose and direct comparisons in patients with cerebrovascular (5–7) or peripheral vascular (8) disease. There have been only two small direct comparisons of low and intermediate aspirin doses in patients with ACS, only one of which has been published (9). These failed to detect an effect of aspirin dose on outcome; however, they had extremely limited statistical power to do so. Furthermore, the assumption that low-dose aspirin has equivalent efficacy in different vascular beds may not be entirely valid. Platelet activation is enhanced in patients with unstable angina or acute MI (10), and the risk of recurrent ischemic events in this population is high. The phenomenon of "aspirin resistance," defined as failure to achieve adequate suppression of biochemical markers of aspirin's inhibition, is observed in up to 20% (11,12) of patients with ACS and has recently been linked to adverse clinical outcome (13,14). There is some evidence that increasing aspirin dose, even within the range 75 to 300 mg

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Abbreviations and Acronyms

ACS	= acute coronary syndrome
ALDUSA	= Aspirin at Low Dose in Unstable Angina
ATACS	= Antithrombotic therapy in Acute Coronary Syndromes Study Group
CARS	= Coumadin Aspirin Reinfarction Study
CHAMP	= Combination Hemotherapy and Mortality Prevention
CI	= confidence interval
DUCCS-II	= Duke University Clinical Cardiology Group Study-II
ECG	= electrocardiographic
GUSTO IIb	= Global Use of Strategies to open Occluded coronary Arteries
HR	= hazard ratio
MI	= myocardial infarction
PURSUIT	= Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrelin Therapy
TxA2	= thromboxane A2

(15,16), may overcome biochemical evidence of aspirin resistance and thus may alter clinical outcome. In order to address this issue we compared six-month ischemic events in patients discharged while receiving low (<150 mg) and intermediate (≥150 mg) aspirin therapy in the Global Use of Strategies to open Occluded coronary Arteries (GUSTO) IIb and Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrelin Therapy (PURSUIT) trials.

METHODS

Patient population. The GUSTO IIb and PURSUIT trials have been described previously (17,18). Briefly, these were large randomized trials in patients with ACS. The GUSTO IIb (n = 12,142) trial recruited patients with non–ST- or ST-segment elevation MI or unstable angina whereas the PURSUIT (n = 10,948) trial enrolled patients with non–ST-segment elevation ACS. In GUSTO IIb patients were required to have chest pain within 12 h of enrollment associated with electrocardiographic (ECG) changes. In PURSUIT patients were recruited within 24 h of their last episode of chest pain at rest and were required to have ECG changes or elevation of creatine kinase-MB fraction. Only patients who survived to hospital discharge were included in this analysis. In GUSTO IIb 495 patients died before hospital discharge, whereas in PURSUIT 324 died before discharge.

Treatment. In GUSTO IIb patients were randomized to intravenous unfractionated heparin or the direct thrombin inhibitor hirudin. Thrombolytic therapy, either streptokinase or an accelerated infusion of tissue plasminogen activator, was given to patients with ST-segment elevation at the discretion of the treating physician. In PURSUIT patients were randomized to one of two doses of the intravenous platelet glycoprotein IIb/IIIa receptor antagonist, eptifibatide, or placebo. In both trials the randomized infusions were continued until hospital discharge or for a maximum of 72 h. In PURSUIT aspirin doses between 80 and 325 mg were recommended. No recommendations on aspirin dose were made in GUSTO IIb. Initial and subsequent in-hospital aspirin dose was recorded in GUSTO IIb. Initial and discharge aspirin dose was recorded in PURSUIT. The subsequent in-hospital aspirin dose recorded in GUSTO IIb was assumed to be the discharge dose for the purpose of this analysis. Coronary revascularization procedures and other treatments were performed at the discretion of the treating physician.

End points. The primary end point of our analysis was the occurrence of the combined end point of death, MI, or stroke between hospital discharge and six months follow-up. Secondary end points included the individual components of the primary end point. In GUSTO IIb, in North America and Australia, all suspected ischemic events between discharge and 30 days were adjudicated by a clinical events committee. In Europe, ischemic events within 30 days were reviewed by an on-site medical monitor. In PURSUIT all MIs and stroke occurring within the first 30 days were adjudicated by a clinical events committee. The MIs between day 30 and 6 months were confirmed but not adjudicated.

Statistical analysis. For the demographic, treatment, and medication summaries, categorical data are presented as frequencies and percentages and continuous data are presented as medians and interquartile ranges. Chi-square tests were used to compare frequencies and Wilcoxon two-sample tests were used to compare the continuous variables. Kaplan-Meier methods were used to estimate the unadjusted six-month event rates and log-rank tests were used to formally compare the groups.

In order to adjust for potential bias in the choice of discharge aspirin dose, a logistic model was used to calculate a propensity score (or probability) that a patient would receive a discharge aspirin dose of ≥150 mg. All demographic/baseline factors in addition to initial aspirin dose (<150 mg vs. ≥150 mg), pre-randomization, index hospitalization and discharge medications, and index hospitalization procedures were considered as possible predictors in the logistic model. Two-way interactions between all factors were also evaluated. The ability of the model to discriminate between patients discharged while receiving <150 mg versus ≥150 mg aspirin was assessed with the c-statistic (equivalent to the area under the receiver operating characteristic curve).

Multiple Cox proportional hazards models of the primary end point and the individual components of this end point were developed. To account for patients who died early and therefore did not have a chance to experience an MI or stroke, patients who died without experiencing an event before the median time to the event were removed from the MI and stroke analyses (MI, median time to event 36 days, 175 patients removed; stroke, median time to event 68.5 days, 333 patients removed). All demographic and baseline

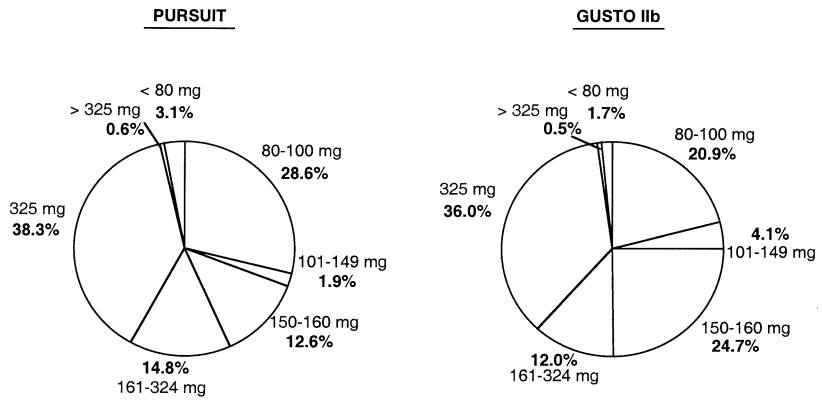

Figure 1. Distribution of aspirin doses in the GUSTO IIb and PURSUIT trials.

factors, index hospitalization and discharge medications, and hospitalization procedures, as well as the propensity score for aspirin dose, were used in the development of the end point models. For continuous variables, if the effect of the variable on the end point was not linear, a cut point was determined in order to fit two linear splines that were then used in the models. For the evaluation of region, the U.S. was used as the reference group. Two-way interactions between aspirin dose and all factors plus other selected two-way interactions were also evaluated. From the adjusted models, hazard ratios (HRs), 95% confidence intervals (CI) of the HRs, and Wald chi-square p values are reported.

To examine the effect of the missing data on the propensity and end point models, data were imputed using medians for the continuous data and modes for the categorical factors. For each outcome, two models were generated using both imputed and non-imputed variables and the results were compared. The impact of the missing data was negligible, as the results of the imputed and non-imputed models were nearly identical. Further, the influence of discharge aspirin dose on outcome did not change between the imputed and non-imputed models. Therefore, the results from the imputed models are provided.

To further evaluate the relationship between aspirin dose and outcome, patients who received a discharge aspirin dose $<$150 mg were matched with patients that received a dose $\geq$150 mg on the basis of similar propensity scores. To determine the matched cohort, patients with propensity scores within 0.01 were randomly matched using a 1:1 ratio. Cox proportional hazards models were then developed within the matched patient cohort and the HRs from these models were compared with those from the overall models.

For all models, trial (PURSUIT vs. GUSTO IIb) was included as a blocking factor as well as a potential covariate. SAS Version 8 Software (Cary, North Carolina) was used to perform all statistical analyses.

RESULTS

Information on discharge aspirin dose and six-month ischemic outcomes was available for 20,521 patients: 96.0% (11,184 of 11,647) of the initial GUSTO IIb population surviving to hospital discharge and 87.9% (9,337 of 10,624) of the initial PURSUIT population surviving to hospital discharge. A discharge aspirin dose $<$150 mg was prescribed to 29.9% (n = 6,128) of patients. The distribution of discharge aspirin doses in the two trials is presented in Figure 1. Baseline characteristics according to aspirin dose are presented in Table 1. There was significant imbalance between the two groups. Patients receiving the higher aspirin dose were younger and more likely to have a history of hypertension, diabetes, hypercholesterolemia, tobacco use or previous MI, coronary artery bypass graft, or coronary angioplasty. In addition, patients discharged while receiving $\geq$150 mg of aspirin were more likely to have ST-segment elevation on their qualifying ECG, rales, and an MI as their enrollment event. A greater proportion of patients receiving the lower aspirin dose were participants in the PURSUIT trial. The majority of patients receiving the lower aspirin dose were recruited in Europe. Apart from beta-blockers and lipid-lowering agents, discharge medications were similar in the two groups.

Six-month outcome. At six months 1,310 patients had a primary event. There was no effect of greater aspirin dose on the combined primary end point of six-month death, MI, or stroke (HR 1.06 [95% CI 0.94 to 1.19], p = 0.35) by univariate analysis. The individual frequencies of death or MI were similar in the two treatment groups; however, stroke was more frequent with the higher aspirin dose (Table 2).

Propensity analysis. Significant predictors of discharge aspirin included in the multivariable logistic propensity model are presented in Table 3. The c-statistic, or area under the receiver operating characteristic curve, was 0.859. This indicates that the model discriminated well between patients discharged while receiving the different aspirin doses.

Multivariable analysis of six-month outcome. Important multivariable predictors of six-month death, MI, and stroke are presented in Table 4. After adjustment for imbalance between the two aspirin groups in these

Table 1. Demographic and Treatment Details

	<150 mg (n = 6,128)	≥150 mg (n = 14,341)
GUSTO IIb*	2,990 (48.8)	8,194 (56.9)
PURSUIT*	3,138 (51.2)	6,199 (43.1)
Study drug*		
Eptifibatide	1,770 (28.9)	3,485 (24.2)
Hirudin	1,449 (23.6)	4,056 (28.2)
Heparin	2,909 (47.5)	6,852 (47.6)
Age (interquartile range)*	65 (56–72)	63.2 (54–71)
Female	1,986 (32.4)	4,504 (31.3)
Caucasian*	5,924 (96.8)	12,792 (88.9)
Region*		
U.S.	463 (7.6)	6,393 (44.4)
Canada	16 (0.3)	1451 (10.1)
Latin America	62 (1.0)	448 (3.1)
Western Europe	4,876 (79.6)	4,147 (28.8)
Eastern Europe	513 (8.4)	970 (6.7)
Australia/New Zealand	198 (3.2)	984 (6.8)
Hypertension*	2,703 (44.1)	7,385 (51.3)
Diabetes*	1,085 (17.7)	2,934 (20.4)
Current smoker*	1,965 (32.2)	5,012 (34.9)
Hypercholesterolemia*	2,283 (37.4)	6,007 (42.0)
Previous MI*	1,952 (31.9)	4,873 (33.9)
Prior stroke	133 (2.2)	356 (2.5)
Prior PTCA*	1533 (25.0)	5065 (35.2)
Prior CABG*	1,170 (19.1)	3,298 (22.9)
Enrollment MI*	3,058 (49.9)	7,786 (54.2)
Qualifying ECG		
ST-segment elevation*	1,617 (26.4)	4,359 (30.3)
T-wave inversion*	2,808 (45.9)	6,370 (44.3)
ST-segment depression*	3,294 (53.8)	7,039 (49.0)
Peripheral vascular disease	468 (7.6)	1,146 (8.0)
Medications on discharge		
ACE inhibitor	1,700 (27.8)	3,918 (27.2)
Beta-blockers*	3,762 (61.6)	8,473 (59.0)
Calcium blockers	2,038 (33.3)	4,806 (33.4)
Lipid-lowering agent*	1,046 (17.1)	2,670 (18.6)
Nitrates	3,400 (55.6)	7,869 (54.8)

*$p < 0.05$. Data are presented as n (%).
ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; ECG = electrocardiogram; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

variables and the propensity for a discharge aspirin dose ≥150 mg, there was no effect of greater discharge aspirin dose on the combined primary end point (HR 0.92 [95% CI 0.79 to 1.07], p = 0.28). However, the higher aspirin dose was associated with a reduction in six-month MI (HR 0.79 [95% CI 0.64 to 0.98], p = 0.03) but a trend towards higher stroke (HR 1.59 [95% CI 0.95 to 2.65], p = 0.08). Aspirin dose did not affect the individual end point of six-month mortality (HR 0.89 [95% CI 0.72 to 1.10], p = 0.30, Fig. 2).

Matched propensity analysis. In order to better adjust for the baseline imbalances between the groups, patients were matched on the basis of propensity score in a 1-to-1 fashion. This limited the analysis to 8,531 patients with 492 events. These patients were well matched on the basis of baseline characteristics. In this matched analysis, there was no difference in the incidence of the composite endpoint death, MI, or stroke at six months (HR 0.94 [95% CI 0.80 to 1.12], p = 0.51). The effect of aspirin dose on the six-month MI (HR 0.83 [95% CI 0.66 to 1.05], p = 0.12) was no longer evident; however, doses ≥150 mg were associated with an increase in the risk of six-month stroke (HR 1.74 [95% CI 1.01 to 3.02], p = 0.05, Fig. 3).

DISCUSSION

In this, the largest study to date examining the relationship between aspirin dose and clinical outcome after ACS, we observed no difference in the combined incidence of death, MI, or stroke among patients discharged while receiving ≥150 mg versus <150 mg per day. Aspirin doses between 75 and 325 mg are currently recommended after an episode of unstable angina or acute MI (2,3). Doses at the lower end of this range are often advocated in order to limit gastrointestinal toxicity (4). The evidence to support these recommendations is drawn from controlled trials of daily aspirin doses of 75 mg (n = 796) (19), 160 mg (n = 17,187) (20), 324 mg (n = 1,266) (21), 650 mg (n = 484) (22), and 1,300 mg (n = 555) (23). However, little is known of the comparative efficacy of aspirin doses within this range. There have been only two small studies that have directly compared aspirin dose in patients with ACS: the Duke University Clinical Cardiology Group Study-II (DUCCS-II, n = 162) and the Aspirin at Low Dose in Unstable Angina (ALDUSA) pilot study (n = 112). The DUCCS-II study compared the efficacy of low (81 mg) and intermediate (325 mg) aspirin doses in patients with acute MI treated with front loaded tissue-plasminogen activator (tPA) or anisoylated plasminogen streptokinase activator complex (APSAC) (9), whereas the ALDUSA pilot study compared daily aspirin doses of 325 mg and 40 mg. Both failed to demonstrate an effect of aspirin dose on outcome but were considerably underpowered to do so. The combination of low-dose aspirin (80 to 81 mg) and warfarin has been

Table 2. Ischemic Outcomes at Six-Month Follow-Up

	Aspirin < 150 mg n/N (KM Est)	Aspirin ≥150 mg n/N (KM Est)	p Value
Death, MI, or stroke	374/6,128 (6.21)	936/14,393 (6.61)	0.34
Death	194/6,107 (3.22)	433/14,360 (3.06)	0.50
MI	209/6,084 (3.50)	515/14,262 (3.69)	0.61
Stroke	28/6,019 (0.48)	102/14,169 (0.74)	0.04

Data are presented as n (%).
MI = myocardial infarction.

Table 3. Variables Included in the Propensity Analysis for Discharge Aspirin Doses ≥150 mg

	Odds Ratio	95% CI	p Value
PURSUIT (vs. GUSTO IIb)	0.46	(0.38–0.55)	< 0.001
Region of enrollment			
Canada	4.99	(3.00–8.30)	< 0.001
Latin America	0.52	(0.38–0.72)	< 0.001
Western Europe	0.05	(0.05–0.06)	< 0.001
Eastern Europe	0.15	(0.13–0.18)	< 0.001
Australia	0.29	(0.24–0.36)	< 0.001
Female (vs. male)	0.83	(0.75–0.92)	< 0.001
Age			
<65 (linear spline)	0.99	(0.99–1.00)	0.016
≥65 (linear spline)	0.99	(0.99–1.01)	0.833
Weight			
<80 (linear spline)	0.99	(0.98–0.99)	< 0.001
≥80 (linear spline)	1.00	(0.99–1.01)	0.848
Systolic blood pressure			
<140 (linear spline)	1.00	(0.99–1.00)	0.084
≥140 (linear spline)	1.00	(0.99–1.00)	0.018
Diastolic blood pressure			
<80 (linear spline)	1.01	(1.01–1.02)	< 0.001
≥80 (linear spline)	1.00	(1.00–1.01)	0.207
Heart rate	1.00	(0.99–1.00)	0.042
T-wave inversion on qualifying ECG	0.79	(0.71–0.89)	< 0.001
Hypertension	1.11	(1.02–1.21)	0.017
Previous angina	0.80	(0.71–0.90)	< 0.001
Peripheral vascular disease	1.24	(1.08–1.44)	0.003
Hypercholesterolemia	1.17	(1.08–1.28)	< 0.001
History of MI	1.15	(1.05–1.26)	0.002
Prior congestive heart failure	0.82	(0.70–0.96)	0.012
Initial aspirin dose ≥150 (vs. <150)	13.23	(11.59–15.11)	< 0.001
ACE inhibitor at baseline	1.21	(1.08–1.36)	0.001
Beta blocker therapy at baseline	1.11	(1.02–1.21)	0.017
Lipid-lowering therapy at baseline	1.18	(1.00–1.38)	0.046
In-hospital lipid-lowering therapy	0.65	(0.53–0.79)	< 0.001
ACE inhibitor at discharge	0.90	(0.82–0.99)	0.023
Beta-blockers at discharge	0.82	(0.76–0.89)	< 0.001
Lipid-lowering therapy at discharge	1.21	(1.00–1.46)	0.050
Thrombolysis administered	0.76	(0.66–0.86)	< 0.001
In-hospital PTCA	1.32	(1.20–1.45)	< 0.001
In-hospital CABG	0.67	(0.59–0.76)	< 0.001
PURSUIT/qualifying ECG T-wave*	1.32	(1.13–1.55)	< 0.001
PURSUIT/previous angina*	1.22	(1.02–1.47)	0.027
PURSUIT/thrombolysis*	1.82	(1.19–2.78)	0.006
Female/thrombolysis*	0.74	(0.58–0.94)	0.014

*Interactions.
CI = confidence interval; other abbreviations as in Table 1.

compared to intermediate (160 to 325 mg) doses in two larger trials, the Coumadin Aspirin Reinfarction Study (CARS, n = 8,803) (24) and the Combination Hemotherapy and Mortality Prevention (CHAMP, n = 5,059) study (25), and in the small (n = 93) pilot trial of the Antithrombotic therapy in Acute Coronary Syndromes Study Group (ATACS) (26). These trials failed to demonstrate an effect of aspirin dose on outcome; however, the use of warfarin in the low-dose aspirin arms may have confounded the comparison of aspirin dose in these trials.

In the recent Antithrombotic Trialists' Collaboration (1), the proportional reduction in vascular events was equivalent for doses of 75 to 150 mg, 160 to 325 mg, and 500 to 1,500 mg daily. However, the majority of the data used in this analysis was drawn from trials of low-dose aspirin in cerebrovascular or peripheral vascular disease. Here aspirin doses as low as 30 to 50 mg daily (5,8) have been extensively studied and provide equivalent protection from death, non-fatal stroke, or MI as higher doses. Kong et al. (27), using random effects models, have re-examined the Antithrombotic Trialist's data. In an unadjusted analysis they demonstrate a lesser effect with increasing aspirin dose, emphasizing the uncertainty. Thus, in the absence of definitive data it has been assumed that the efficacy of low-dose aspirin is equivalent in different vascular beds. This assumption may not be entirely valid, as platelet

Table 4. Important Multivariable Predictors of Six-Month Death, MI, or Stroke

Predictor	Hazard Ratio	95% CI
PURSUIT	1.26	1.10–1.43
Region of enrollment Western Europe	0.74	0.59–0.94
Female	0.81	0.71–0.92
Qualifying ECG ST depression	1.34	1.20–1.51
Enrollment MI	1.31	1.17–1.47
Presence of rales	1.17	1.01–1.36
Renal insufficiency	2.11	1.46–3.05
Diabetes	1.54	1.36–1.74
Previous angina	1.36	1.18–1.58
Peripheral vascular disease	1.18	1.00–1.40
History of MI	1.50	1.34–1.68
Prior stroke	1.56	1.22–1.99
Current smoker	1.35	1.18–1.54
In-hospital PTCA	0.73	0.63–0.84
In-hospital CABG	0.45	0.36–0.55

In addition to the propensity score, the adjusted model included Canada, Latin America, Eastern Europe, Australia, age, weight, systolic blood pressure, heart rate, family history of CAD, in-hospital ACE and discharge lipid lowering therapy.
Abbreviations as in Tables 1 and 3.

activation is enhanced in unstable angina or acute MI and the risk of recurrent ischemic events is high in this population (10).

Aspirin exerts its antithrombotic effect through irreversible inhibition of the enzyme cyclo-oxygenase-1 (28), also referred to as prostaglandin H synthase. Aspirin acetylates a serine residue within the active site of the enzyme preventing access of its substrate arachidonic acid thus inhibiting the production of thromboxane A2 (TxA2), a potent platelet agonist. Aspirin doses ≥100 mg provide near complete suppression (95 ± 4%) of TxA2 production in clotted whole blood in healthy individuals (29). However, persistent TxA2 production, as evidenced by urinary excretion of TxA2 metabolites, has been documented in up to 20% of ACS patients despite aspirin therapy (11). This failure to achieve complete inhibition of TxA2 production, often referred to as "aspirin resistance," has recently been linked to adverse clinical outcome (14). In the Heart Outcomes Prevention Evaluation (HOPE) study, elevated urinary concentrations of 11-dehydro thromboxane B2, a stable metabolite of TxA2, were associated with an increased risk of cardiovascular death and MI (13). The cause of aspirin resistance is unknown; however, aspirin's inhibition of urinary thromboxane B2 excretion is dose dependent between 20 mg and 325 mg of aspirin (15), and in some situations ex vivo evidence of aspirin resistance can be overcome by increasing dose (16). Although these data would suggest that aspirin doses ≥150 mg might be particularly important in ACS, where aspirin resistance is common, we observed no significant benefit yet significantly greater risk with higher aspirin doses. Other investigators (30,31) have performed analyses of aspirin dose on adverse outcome after an ACS. In an analysis of more than 12,000 patients in the CURE trial, low-dose aspirin (<100 mg) was associated with a substantially lower risk of bleeding. Similarly, in a meta-analysis of more than 300,000 patients, Serebrauny et al. (31) observed that higher aspirin doses were associated with more frequent bleeding. Unfortunately, data on long-term bleeding were not recorded in PURSUIT and GUSTO IIb. It remains plausible that, in our study, higher aspirin dose was associated with an increase in six-month stroke in unadjusted and matched analyses as a result of increased bleeding risk.

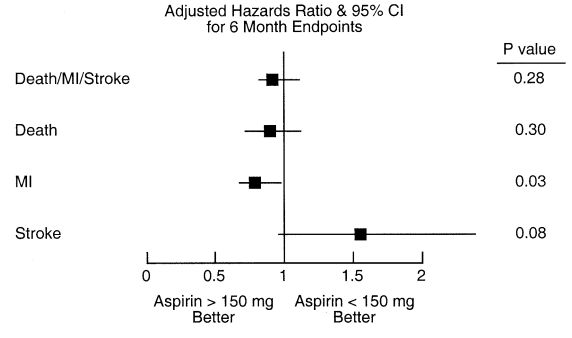

Figure 2. Multivariate adjusted hazard ratios for six-month death, non-fatal myocardial infarction (MI), and stroke. CI = confidence interval.

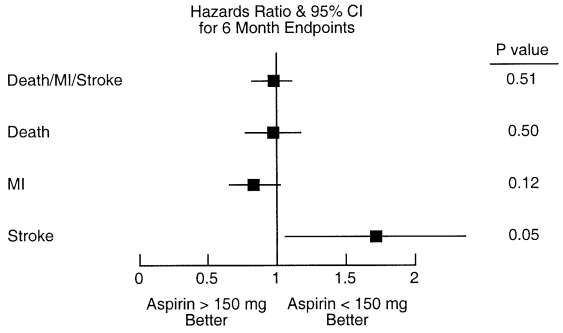

Figure 3. Hazard ratios for six-month death, non-fatal myocardial infarction (MI), and stroke after matching on the basis of the propensity score. CI = confidence interval.

Our findings are non-randomized and cannot be considered conclusive. It is possible that patients perceived to be at increased risk of stroke were prescribed a higher dose of aspirin. Furthermore, we cannot exclude dose changes or variation in compliance after discharge. For example, the patients in the lower aspirin dose may have been prescribed the lower dose because of intolerance and potentially been less compliant. These limitations emphasize the need for a large dedicated randomized trial to fully examine this issue. Although the effect of aspirin dose on outcome may be small, it is important to realize that it may have profound implications because of the high prevalence of coronary artery disease and associated aspirin use. There is evidence that aspirin's gastrointestinal side effects are dose dependent (32), higher doses being associated with increased risk. The recent CURE trial findings in a large cohort reinforce the liability of higher dose aspirin, such as 325 mg, for predisposition to bleeding complications.

Conclusions. In this pooled analysis of more than 20,000 patients with unstable angina or acute MI, we observed no difference in the incidence of death but, potentially, less frequent MI and more frequent stroke among patients discharged while receiving higher aspirin doses. Given the enormous epidemic of atherosclerosis and its complications, identifying the appropriate dose of aspirin in the low-dose range could have a much larger impact on death and disability than many newer treatments.

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REFERENCES

1. Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71–86.
2. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non–ST-segment elevation myocardial infarction: executive summary and recommendations. Circulation 2000;102:1193–209.
3. Bertrand ME, Simoons ML, Fox KA, et al. Management of acute coronary syndromes: acute coronary syndromes without persistent ST-segment elevation; recommendations of the Task Force of the European Society of Cardiology. Eur Heart J 2000;21:1406–32.
4. Roderick PJ, Wilkes HC, Meade TW. The gastrointestinal toxicity of aspirin: an overview of randomised controlled trials. Br J Clin Pharmacol 1993;35:219–26.
5. The Dutch TIA Trial Study Group. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. N Engl J Med 1991;325:1261–6.
6. Taylor DW, Barnett HJ, Haynes RB, et al. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomized controlled trial. Lancet 1999;353:2179–84.
7. UK-TIA Study Group. United Kingdom transient ischemic attack (UK-TIA) aspirin trial: interim results. Br Med J 1988;296:316–20.
8. Ranke C, Creutzig A, Luska G, et al. Controlled trial of high- versus low-dose aspirin treatment after percutaneous transluminal angioplasty in patients with peripheral vascular disease. Clin Invest 1994;72:673–80.
9. O'Connor CM, Meese RB, McNulty S, et al. Randomized factorial trial of reperfusion strategies and aspirin dosing in acute myocardial infarction. The DUCCS-II Investigators. Am J Cardiol 1996;77:791–7.
10. Fitzgerald DJ, Roy L, Catella F, FitzGerald GA. Platelet activation in unstable coronary disease. N Engl J Med 1986;315:983–9.
11. Cipollone F, Patrignani P, Greco A, et al. Differential suppression of thromboxane biosynthesis by indobufen and aspirin in patients with unstable angina. Circulation 1997;96:1109–16.
12. Vejar M, Fragasso G, Hackett D, et al. Dissociation of platelet activation and spontaneous myocardial ischemia in unstable angina. Thromb Haemost 1990;63:163–8.
13. Eikelboom JW, Hirsh J, Weitz JI, Johnston M, Yi Q, Yusuf S. Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. Circulation 2002;105:1650–5.
14. Gum PA, Kottke-Marchant K, Welsh PA, White J, Topol EJ. A prospective, blinded determination of the natural history of aspirin resistance among stable patients with cardiovascular disease. J Am Coll Cardiol 2003;41:961–5.
15. FitzGerald GA, Oates JA, Hawiger J, et al. Endogenous biosynthesis of prostacyclin and thromboxane and platelet function during chronic administration of aspirin in man. J Clin Invest 1983;71:676–88.
16. Cooke GE, Liu-Stratton Y, Frid DJ, Magorien RD, Bray PF, Goldschmidt-Clermont PJ. Pharmacogenomics: response to aspirin is dose, agonist, and PLA dependent. J Am Coll Cardiol 2001;37 Suppl A:1A–648A.
17. The GUSTO IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. N Engl J Med 1996;335:775–82.
18. The PURSUIT Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Engl J Med 1998;339:436–43.
19. The RISC Group. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. Lancet 1990;336:827–30.
20. ISIS-2 Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected myocardial infarction: ISIS-2. Lancet 1988;ii:349–60.
21. Lewis HD, Jr., Davis JW, Archibald DG, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. N Engl J Med 1983;309:396–403.
22. Theroux P, Waters D, Qiu S, McCans J, de Guise P, Juneau M. Aspirin versus heparin to prevent myocardial infarction during the acute phase of unstable angina. Circulation 1993;88:2045–8.
23. Cairns JA, Gent M, Singer J, et al. Aspirin, sulfinpyrazone, or both in unstable angina. Results of a Canadian multicenter trial. N Engl J Med 1985;313:1369–75.
24. Coumadin Aspirin Reinfarction Study (CARS) Investigators. Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. Lancet 1997;350:389–96.
25. Fiore LD, Ezekowitz MD, Brophy MT, Lu D, Sacco J, Peduzzi P. Department of Veterans Affairs Cooperative Studies Program Clinical Trial comparing combined warfarin and aspirin with aspirin alone in survivors of acute myocardial infarction: primary results of the CHAMP study. Circulation 2002;105:557–63.
26. Cohen M, Adams PC, Hawkins L, Bach M, Fuster V. Usefulness of antithrombotic therapy in resting angina pectoris or non–Q-wave myocardial infarction in preventing death and myocardial infarction. Am J Cardiol 1990;66:1287–92.
27. Kong DF, Hasselblad V, Kandzari DE, Newby LK, Califf RM. Seeking the optimal aspirin dose in acute coronary syndromes. Am J Cardiol 2002;90:622–5.
28. Vane J. Inhibition of prostaglandin biosynthesis as a mechanism of action of aspirin-like drugs. Nature 1971;231:232–5.
29. Patrignani P, Filabozzi P, Patrono C. Selective cumulative inhibition of platelet thromboxane production by low-dose aspirin in healthy subjects. J Clin Invest 1982;69:1366–72.
30. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494–502.
31. Serebruany VL, Malinin AI, Sane DC. The risk of bleeding complications with antiplatelet agents: a meta-analysis of 338,191 patients enrolled in 50 randomized controlled trials. Circulation 2003;106:II721.
32. Slattery J, Warlow CP, Shorrock CJ, Langman MJ. Risks of gastrointestinal bleeding during secondary prevention of vascular events with aspirin—analysis of gastrointestinal bleeding during the UK-TIA trial. Gut 1995;37:509–11.